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10/761,634	01/21/2004	Raghavan Rajagopalan	MRD / 69DV	3347

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EXAMINER	
SAUNDERS, DAVID A	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/27/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/761,634	RAJAGOPALAN ET AL.	
	Examiner	Art Unit	
	David A. Saunders, PhD	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *8-16 and 22-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

STATUS OF CLAIMS

Amendment of 10/16/06 has been entered. Claims 1-27 are pending. The amendment has added no new matter; the addition to the specification and the changes in the claims are supported by Pat 5,518,888, which was incorporated by reference at specification page 12. It is noted that Pat 5,518,888 was incorporated by reference in the precise context of a discussion of the biological receptors recited in the Markush group of instant claims 1 and 18.

ELECTION

Applicant's election of Group I (claims 1-7 and 17-21) in the reply filed on 10/16/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election of a heat stable toxin as the receptor is acknowledged. The examiner will, however, cite prior art pertaining to the other receptors of instant claims 1 and 18, should applicable prior art be found among references submitted by applicant or searched by the examiner.

OBJECTIONS TO SPECIFICATION

The disclosure is objected to because of the following informalities: At page 1, line 4 "now pending" must be changed to –now abandoned--.

Appropriate correction is required.

OBJECTIONS TO CLAIMS

Claim I is objected to under 37 CFR 1.75(i), as being of improper form for failing to indent each active verb step. Step d) improperly has two distinct steps of "preparing" and "isolating". Step f) improperly has two steps of "administering" and "allowing".

REJECTIONS UNDER 112, SECOND PARA.

Claims 1-7 and 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing by variously reciting "internal image antibody" in the singular (e.g. in preamble) and "internal image antibodies" in the plural (e.g. in step e)). Consistency is required

In claim 1, step d), "the internal image anti-receptor antibodies" lack antecedent basis in the body of the claim.

In claim 1, step f), "in step e)" is unclear. It is believed that applicant intends to recite –of step e)--.

In claim 1, step f), "effective concentration" is unclear because there is no statement of what effect is to be achieved.

In claim 2, "intermediates" are unclear. What are these "intermediates" of? Furthermore, the term "biosynthetic intermediates" is overly broad and relative, since one does not know how many steps away from the biosynthesis of a given ligand a "biosynthetic intermediate" can be and still be considered as a "biosynthetic intermediate". For example, cholesterol is a "biosynthetic" precursor for numerous steroid ligands. Among the precursors of Cholesterol are acetyl-CoA and acetoacetyl Co-A. How far back from any given steroid can one go in its biosynthetic pathway and still have a precursor that is a "biosynthetic intermediate"?

In claim 17 recitation of "photodiagnostic composition" is unclear because only a conjugate of an antibody and a photoactive dye (i.e. one compound) is recited. A "composition" would have more than one compound. What else is in the composition?

REJECTIONS UNDER 112, FIRST PARA.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant was not in possession of either the subgenus of nucleosides or the subgenus of biosynthetic intermediates, recited in the Markush group of claim 2.

With respect the ligands that are nucleosides, the examiner finds that no receptor recited in the Markush group of base claim 1 would have a nucleoside as a cognate ligand. For example, steroid receptor ligands do not have a structure like that of any nucleoside; thus no nucleoside would bind to a steroid receptor. Thus one of skill would not be able to envision a nucleoside which can bind to any steroid receptor. Even if one could possibly find such a nucleoside with extensive screening therefor by binding assays, it is to be noted that any screening method that one of skill might know of, would not provide a description of the products that would be identified by any screening method. Like considerations apply to the binding of nucleosides to all other receptors recited in the Markush group of base claim 1.

With respect the ligands that are "biosynthetic intermediates", the examiner finds this subgenus is overly broad and not defined. This subgenus would thus include numerous members that would not bind to any receptor recited in the Markush group of base claim 1. For example, numerous steroid receptors would not bind cholesterol as a cognate ligand, yet cholesterol is a biosynthetic precursor for numerous steroid ligands, each of which have their own unique receptors. Among the precursors of Cholesterol are acetyl-CoA and acetoacetyl Co-A, yet neither of these would bind to a steroid receptor. Again, even if one could screen for "biosynthetic intermediates" which would bind to a given steroid receptor by binding assays, it is to be noted that any screening method that one of skill might know of, would not provide a description of the products that would be identified by any screening method. Like considerations apply to the binding of "biosynthetic intermediates" to all other receptors recited in the Markush group of base claim 1.

Claims 1-7 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the case in which the receptor is an extracellular/cell surface receptor, does not reasonably provide enablement for the case in which the receptor is an intracellular/nuclear receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Of the receptors recited in the Markush group of instant claims 1 and 18, it is art known that steroid receptors are intracellular/nuclear receptors. See discussion of Evans et al (5,571,696) at col. 1, lines 38-48 and col. 2, lines 53-63. It is also art known that antibodies, as well as the smaller Fab fragments thereof, are unable to penetrate the cell membrane. The only antibodies that are able to localize intracellularly are antibodies that bind to a cell surface receptor which can internalize and carry the bound antibody into the cell interior. Since it is not possible for antibodies to penetrate the cell membrane in order to bind to a nuclear receptor, such as a steroid receptor, applicant's invention is not enabled for the case in which the receptor is an intracellular/nuclear receptor. Since the Markush group of claims 1 and 18 is large, and since only the heat-stable toxin receptor was elected, the examiner has not determined whether there may be other recited receptors which, like the steroid receptor, are also intracellular/ nuclear receptors. It is, therefore, applicant's responsibility to delete all receptors recited in the Markush group that may also be intracellular/nuclear receptors.

Claims 2 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the case in which the receptor-binding ligand is selected from the group consisting of drugs, hormones, peptides, carbohydrates, peptidomimetics, and glycomimetics, does not reasonably provide enablement for the case in which the receptor-binding ligand is selected from the group consisting of nucleosides and biosynthetic intermediates. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

With respect the ligands that are nucleosides, the examiner finds that no receptor recited in the Markush group of base claim 1 would have a nucleoside as a cognate ligand. For example, steroid receptor ligands do not have a structure like that of any nucleoside; thus no nucleoside would bind to a steroid receptor. Thus one of skill would not reasonably expect to find a nucleoside which can bind to any steroid receptor, even with extensive screening. Like considerations apply to the binding of nucleosides to all other receptors recited in the Markush group of base claim 1.

With respect the ligands that are "biosynthetic intermediates", the examiner finds this subgenus is overly broad and would include numerous members that would not bind to any receptor recited in the Markush group of base claim 1. For example, numerous steroid receptors would not bind cholesterol as a cognate ligand, yet cholesterol is a biosynthetic precursor for numerous steroid ligands, each of which have their own unique receptors. Among the precursors of Cholesterol are acetyl-CoA and acetoacetyl Co-A, yet neither of these would bind to a steroid receptor. Like considerations apply to the binding of "biosynthetic intermediates" to all other receptors recited in the Markush group of base claim 1.

ANTICIPATION

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 17-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Rajagopalan (WO 93/00934).

Rajagopalan teaches immunodiagnostic reagents for in vivo imaging. He provides precisely the same motivation as taught instantly for using anti-Id Abs as internal images to target a receptor (e.g. see para. Spanning pages 2-3 and 4-5). He teaches targeting of glucocorticoid (i.e. steroid) receptors at page 1 and digoxin (i.e. a cardiac glycoside) receptors at page 10. He teaches that the anti-Id Ab may be conjugated to a europium chelate fluorescent label (page 10, line 8). The examiner considers that, for the purposes of diagnostic imaging, the europium chelate can be properly considered to be within the scope of a "photoactive dye" as recited in instant claim 17.

OBVIUOSNESS

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rajagopalan in view of Ballou et al (Cancer Immunol Immunother 41,257,1995 (ref BT)).

Rajagopalan has been cited supra as anticipating claims 17-18 and 20. Ballou et al teach that cyanine dyes are preferred labels for in vivo imaging. It thus would have been obvious to have substituted a cyanine dye, in lieu of the europium chelate, taught by Rajagopalan. This basis of rejection is made in the event that applicant might not consider the europium chelate to be properly considered as a "photoactive dye" as required by claim 17.

Regarding dependent claim 19, note the excitation wavelengths of cyanine dyes taught by Ballou et al at page 258, col. 2.

Regarding dependent claim 21, note the teachings of administration of "10-100 ug conjugated antibody" by Ballou et al at page 258, col. 2, under "Imaging". If one considers that the mid-range of 55 ug conjugated antibody was administered to a typical mouse weighing ~1 oz (~27 g), then Ballou et al administered antibody conjugate at a dose of 55ug/ 27g, which reduces to a dose of ~2mg/Kg, which is well within the range recited in claim 21. Though the antibodies used in the imaging method of Ballou et al are not anti-Id Abs, the dosages taught by Ballou et al would have been expected to also be applicable to anti-Id Abs, because of the fact that anti-Id Abs and the antibodies used by Ballou et al would be of the same approximate molecular weight.

Claims 1-7 and 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rajagopalan in view of Goldenberg (5,716,595).

Rajagopalan has been noted supra for teaching immunodiagnostic methods using anti-Id Abs as internal images for targeting a receptor (e.g. see para. Spanning pages 2-3 and 4-5) and for teaching targeting of glucocorticoid (i.e. steroid) receptors at page 1 and digoxin (i.e. a cardiac glycoside) receptors at page 10. He has also been noted for teaching that the anti-Id Ab may be conjugated to a europium chelate fluorescent label (page 10, line 8).

With respect to steps a)-c) of instant claim 1, it is inherent that one would be required to select a ligand, such as one of those taught by Rajagopalan at page 1, and to prepare it as an antigen, in order to raise monoclonal antibodies thereto. For example, it is inherent that monoclonal anti-digoxin antibody obtained from a commercial source (page 11, lines 14-15) would have been obtained by preparing digoxin as an antigen for immunizing Balb-C mice, in order to obtain a monoclonal anti-digoxin antibody ("first generation antibody"); see, for example, Goldenberg at col. 12, lines 58-65 for a teaching of how monoclonal antibodies are conventionally made. It is also inherent that any manufacturer

would provide monoclonal antibodies that have been "isolated" to some degree from the ascites fluid or culture fluid into which they have been secreted.

With respect to step d) of instant claim 1, Rajagopalan prepares monoclonal anti-Id Abs against the monoclonal anti-digoxin Ab in Examples 1-2.

With respect to step e) of instant claim 1, Rajagopalan teaches conjugation of a chelator to the anti-Id Ab, and teaches that the chelator, in turn, can be complexed with europium for immunofluorescent imaging (page 10, lines 7-8 and page 14, lines 4-9). Furthermore, Goldenberg teaches the conjugation of monoclonal antibodies with photoactive molecules that are employed in a method of in vivo imaging. Though the antibodies used in the imaging method of Goldenberg are not anti-Id Abs, the conjugation methods applied to any antibody are also applicable to anti-Id Abs, because of the fact that conjugation of any kind of label to an antibody is conducted so that the conjugation occurs outside of the antigen binding site of the Ab (e.g. note Rajagopalan at page 4, lines 25-28 and Goldenberg at col. 9, lines 25-48).

With respect to steps f)-g) of instant claim 1, Rajagopalan teaches administration of conjugates so that they accumulate at a target site, where the internal image (anti-Id) Ab binds; see, for example, page 15, line 2-page 16, line 28. Likewise, Goldenberg teaches such administration of conjugates; see, for example, col. 3, line 23-col. 6, line 9. Goldenberg further teaches exposing the accumulated conjugate to irradiation, so that a detectable fluorescence is emitted by the conjugated photoactive molecule; see, for example, col. 11, line 63-col. 12, line 16 and col. 17, lines 35-60.

The method of Claims 1 and 6, thus would have been obvious, as would the more briefly recited method of instant claims 17-18 and 20. The references of Rajagopalan and Goldenberg are properly combinable, since both deal with the in vivo localization/imaging of fluorescent/photoactive labels that are conjugated to antibodies.

Regarding dependent claim(s) 2, the digoxin taught by Rajagopalan is a "drug" and a "carbohydrate".

Regarding dependent claim(s) 3, the DHE dye used by Goldenberg in Example 4 is a porphyrin (see col. 16, lines 65-col. 17, line 3).

Regarding dependent claim(s) 4-5 and 21, note teachings of Goldenberg at col. 17, lines 45-48. Though the antibodies used in the imaging method of Goldenberg are not anti-Id Abs, the dosages taught by Goldenberg would have been expected to also be applicable to anti-Id Abs, because of the fact that anti-Id Abs and the antibodies used by Goldenberg would be of the same approximate molecular weight.

Regarding dependent claim(s) 7, note the teachings of Rajagopalan at page 10, lines 9-16

Regarding dependent claim(s) 19, note teachings of Goldenberg at col. 17, lines 45-48 and in claims 9-16 regarding the imaging of myocardial tissue in order to diagnose "coronary disorders" which term would render numerous embodiments of claim 7 immediately apparent and thus obvious.

In the above rejections, applicable prior art against all claims has been cited that pertains to a receptor other than the elected heat stable toxin receptor. The examiner will not thus not presently search further for art pertaining to the heat stable toxin receptor.

PRIOR ART OF INTEREST

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Carson (4,683,295) teaches the preparation of anti-Id Abs against receptors. He does not teach their use in methods of in vivo imaging.

CONTACTS

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is 571-272-0849. The examiner can normally be reached on Mon.-Thu.

from 8:00 am to 5:30 pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Typed 12/18/06 DAS

David A. Saunders

DAVID A. SAUNDERS
PRIMARY EXAMINER